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REVIEW

Cerebrovascular Complications in Bacterial Meningitis

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The objective is to describe a comprehensive analysis of patients with bacterial meningitis exacerbate by cerebrovascular complications. We reviewed the literature on cerebrovascular complications in adult patients with bacterial meningitis. Cerebrovascular complications occur in one fourth of patients with bacterial meningitis. The most common cerebrovascular disease complicating bacterial meningitis are cerebral infarctions (9%–25%), intracerebral hemorrhage (1%–7%), cerebral venous thrombosis (1%–10%), and subarachnoid hemorrhage (1%–5%). *Streptococcus pneumoniae* and *Staphylococcus aureus* are the primary causative pathogens leading to these complications. The pathophysiological mechanisms have not completely been elucidated but involve vasculitis, endothelial dysfunction, hypercoagulability, aggregation, and complement activation. Cerebrovascular complications are important predictors of unfavorable outcome and death, and the use of adjunctive dexamethasone has been described to reduce the incidence. In conclusion, cerebrovascular complications are common in bacterial meningitis and are strongly associated with unfavorable outcomes and death. Although our understanding of the pathophysiology is evolving, there remains a need for novel treatment strategies to address these complications.

Key Words: bacterial meningitis ■ cerebral venous thrombosis ■ cerebrovascular complication ■ delayed cerebral thrombosis ■ intracerebral hemorrhage ■ streptococcus pneumonia ■ stroke ■ subarachnoid hemorrhage

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Bacterial meningitis remains a life-threatening disease despite the introduction of conjugate vaccines,[1–4] with persistent high mortality and morbidity rates worldwide.[3,5] Cerebrovascular complications, which have been reported in up to 25% to 31% of patients, are important determinants of poor disease outcome.[6–10] Multiple mechanisms have been proposed linking meningitis to cerebrovascular diseases, including activation of coagulation and inhibition of fibrinolysis pathways, inflammation of cerebral arteries, and immune-mediated thrombosis.[11–16] For this narrative review, we searched PubMed for studies on cerebrovascular complications in bacterial meningitis. The following Medical Subject Headings terms were used: bacterial meningitis, stroke, cerebral infarction, transient ischemic attack, delayed cerebral thrombosis, intracerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage, intracranial thrombosis, cerebral venous thrombosis, and central nervous vasculitis. We used only articles written in English and limited the review to adults with bacterial meningitis.

CEREBRAL INFARCTION

Studies have reported varying rates of cerebral infarction in bacterial meningitis. A German retrospective study, involving 87 adults with pneumococcal meningitis, described cerebral infarction to occur in 22%.[6] Outcome was unfavorable in 17 of these patients (94%), and 6 of them died (33%).[6] Another German study, involving 68 adults with pneumococcal meningitis, described cerebral infarction in 9%.[17] This study used magnetic resonance imaging, showing that 50% of the patients had ischemia in the anterior

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circulation and 50% in both the anterior and posterior circulation.[17] All patients with cerebral ischemia in this study had an unfavorable outcome.[17] A Danish cohort study, involving 152 patients, showed cerebral ischemia in 13%.[18] *S. pneumoniae* was the most common causative pathogen (64%), involving more than 1 vascular territory in the majority of the patients (63%).[18] Clinical characteristics associated with cerebral infarctions in this study were advanced age, endocarditis, and presentation in a coma.[18] Patients with infarction were at high risk for unfavorable outcome (86% for those with infarction versus 37% for those without infarction; age-adjusted risk ratio [RR] 2.09, 95% CI 1.59–2.75).[18]

A Dutch prospective nationwide cohort study, involving 696 patients with bacterial meningitis, described cerebral ischemia to occur in 174 (25%).[9] Meningitis in patients with cerebral infarction was most commonly caused by *S. pneumoniae* (74%). Baseline characteristics associated with infarctions were advanced age, immunocompromised state, focal neurologic abnormalities, and lower scores on the Glasgow Coma Scale.[9] This study showed a mortality of 32% in patients with cerebral infarction compared to 17% in patients without cerebral infarction ($P<0.001$).[9] The majority of patients with cerebral infarctions (55%) died due to a neurologic complication, whereas death was due to a systemic cause in most patients without cerebral infarctions. Infarction was related to unfavorable outcome in multivariate analysis (odds ratio [OR] 3.37; 95% CI 2.19–5.21; $P<0.001$).[9] A French cohort study, involving 506 patients with bacterial meningitis, described cerebrovascular complications including cerebral infarctions in 128 patients (25%).[19] The majority of patients were infected by *S. pneumoniae* (63%).[19]

Cerebral infarction may manifest even after the initial recovery period. Delayed cerebral thrombosis, a condition reported in bacterial meningitis, is characterized by an initial good clinical recovery followed days later by an abrupt deterioration caused by cerebral ischemia.[20–22] A Dutch prospective cohort study described delayed cerebral thrombosis in 11 of 1032 patients with bacterial meningitis [21]; 10 patients had pneumococcal meningitis and 1 listeria meningitis.[21] The diagnosis was made following clinical deterioration 7–42 days after disease admission.[21] Patients were ready for discharge or discharged when they suddenly deteriorated with impaired consciousness (73%), focal neurological abnormalities (82%), and seizures (27%).[21] In this study 6 of 11 patients (55%) received high-dose corticosteroids after secondary deterioration, and antibiotic treatment was prolonged or restarted in 4 of them (36%).[21] Ten patients (91%) had unfavorable outcome and 3 of them died (27%).[21] A Spanish observational retrospective multicenter study, involving 162 patients with pneumococcal meningitis, reported delayed cerebral thrombosis in 10% of the patients, but this study used less strict criteria.[23] A retrospective cohort study from the United States in 120 patients with bacterial meningitis showed delayed cerebral thrombosis in 5 (4%) of the patients, (Table and Figure)[22]

CLINICAL PERSPECTIVE

- Cerebrovascular complications are common in patients with bacterial meningitis and are associated with unfavorable outcome and death.
- We recommend conducting neuroimaging in patients with bacterial meningitis and focal neurologic symptoms or altered level of consciousness to identify the underlying cause.

The precise underlying mechanisms of cerebral infarctions remain unclear. A study involving brain autopsies of 31 patients who succumbed to pneumococcal meningitis revealed intriguing findings.[11] Notably, 97% of these cases exhibited vascular inflammation, 77% had parenchymal microhemorrhages, 68% showed evidence of thrombosis, and 61% displayed infarctions. Furthermore, inflammation affecting medium-large arteries resulted in vascular lumen obstruction, leading to cerebral infarctions in 45% of the patients. Additionally, the inflammatory response could induce endothelial dysfunction, intimal thickening, stenosis, dilatation, and edema, all contributing to vascular damage and subsequent cerebrovascular complications.[24]

Inhibition of the fibrinolysis pathway has been associated with cerebral infarctions in patients with bacterial meningitis.[12–14] The activity of tissue plasminogen activator is primarily regulated by plasminogen activator inhibitor type I.[25] A study on plasminogen activator inhibitor type I showed a genetic polymorphism (rs1799889) influenced plasminogen activator inhibitor type I concentrations in cerebrospinal fluid. Higher plasminogen activator inhibitor type I levels were associated with a lower risk of cerebrovascular complications and mortality.[26] A genetic association study in 1101 bacterial meningitis patients evaluated genetic variation in coagulation and fibrinolysis genes that potentially influenced the risk of cerebrovascular complications.[27] Mechanisms such as a hypercoagulable state, resulting in widespread intravascular thrombosis, and vasospasms in the absence of inflammation, also

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contribute to cerebrovascular complications.[15,16] An autopsy study in delayed cerebral thrombosis showed multiple cerebral infarctions with intravascular thrombosis without evidence of vasculitis,[28] suggesting the possibility of thrombotic microangiopathy. In this line, patients with delayed cerebral thrombosis had elevated levels of complement factor 5a in cerebrospinal fluid upon presentation, and increased tissue factor/factor VII activity have also been implied to play a role.[21]

CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis rarely complicates bacterial meningitis. A Dutch nationwide prospective cohort study, involving 2220 patients with bacterial meningitis, demonstrated cerebral venous thrombosis in 1% of the patients.[29] *S. pneumoniae* (65%) and *S. pyogenes* (8%) were the most common causative pathogens.[29] The most common thrombosed sinus was the transverse sinus (69%), followed by the sigmoid sinus 46% and the superior sagittal sinus 27%. Internal jugular vein thrombosis was documented in 15% of the patients, an isolated cortical vein thrombosis in 12%, and cavernous sinus thrombosis in 8%.[29] Additional radiological findings were cerebral infarction(s) in 38%, mastoiditis in 31% and intracerebral hemorrhage in 8%.[29] The diagnosis of cerebral venous thrombosis was often made on presentation (58%). Most patients diagnosed with cerebral venous thrombosis also presented with concurrent sinusitis or otitis (67%). Patients with sinus thrombosis presented more often comatose (53 versus 18%; $P = 0.001$) and, more often developed focal neurologic symptoms (58 versus 22%; $P<0.001$),[29] but the likelihood of dying between patients with and without cerebral venous thrombosis was similar (16%).

A German prospective case series, involving 86 patients, described cerebral venous thrombosis to occur in 4 patients (5%).[16] Two had a superior sagittal sinus thrombosis (50%) and 2 patients a cortical vein thrombosis.[16] Unfavorable outcome was noted in 3 patients (75%).[16] Another German retrospective study, involving 87 patients with pneumococcal meningitis, identified cerebral venous thrombosis in 5%.[6] Unfavorable outcome occurred in 89% of patients and 22% died.[6] An autopsy study showed multifocal deep intramural inflammation of the cerebral venous sinus with the presence of bacteria. Besides hypercoagulability as suggested in earlier studies,[30] direct inflammatory damage to the vessel wall caused by bacterial invasion probably causes cerebral venous thrombosis (Table and Figure).[31]

CEREBRAL HEMORRHAGE

In a Dutch prospective cohort study, involving 2306 patients with bacterial meningitis, intracerebral hemorrhage was identified in 44 (2%) patients and subarachnoid hemorrhage in 22 patients (1%).[32,33] The most common causative pathogen was *S. pneumoniae* followed by *Staphylococcus aureus*. Of the 66 patients, 12 patients underwent computed tomography or magnetic resonance angiography or digital subtraction angiography (18%), and signs of vasculitis were seen in 3 patients (25%).[32,33] The majority of the intracerebral hemorrhages were lobar (70%), followed by deep hemorrhages (9%), infratentorial hemorrhages (11%), and multifocal (micro)hemorrhages (9%).[32] Patients with simultaneous endocarditis (9% versus 1%) or using anticoagulation medication were at risk for intracerebral hemorrhage.[32] Subarachnoid hemorrhage was present on admission in one third of patients and developed in others after a median of 5 days.[33] One patient with subarachnoid hemorrhage (5%) had concomitant endocarditis and a mycotic cerebral aneurysm on computed tomography angiography. Intracerebral and subarachnoid hemorrhage complicating bacterial meningitis was associated with high rates of unfavorable outcome (89% and 86%, respectively) and death (55% and 54%, respectively). None of the patients in these 2 studies had endocarditis and septic arthritis.

A Danish observational retrospective study, involving 152 patients with bacterial meningitis, reported intracerebral hemorrhage in 6 patients (4%) and subarachnoid hemorrhage in 1 patient (1%).[18] The majority of patients had pneumococcal meningitis (64%).[18] A German retrospective multicenter study, involving 87 patients with pneumococcal meningitis, reported intracerebral and subarachnoid hemorrhage in 9% and 2% of the patients, respectively.[6] Six of these 8 patients had signs of vasculitis on additional angiography, including all patients with subarachnoid hemorrhage.[6]

The underlying mechanisms responsible for intracerebral hemorrhage is likely a result of a combination of factors, including inflammation of blood vessels, activation of coagulation pathways, and the inhibition of fibrinolysis, as suggested by prior research.[32,34] A previous study using transcranial Doppler revealed an association between cerebral blood flow velocities indicative of vasculitis and the occurrence of strokes in individuals with bacterial meningitis.[35] Patients with coexisting endocarditis are at risk for intracerebral hemorrhage.[32] In patients with *S. aureus* endocarditis, bacterial meningitis is caused by septic emboli

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Table. Selected Clinical Studies Showing the Frequency of Stroke in Patients With Bacterial Meningitis

Author/year of publication	Study design	Definition of stroke	Frequency of cerebral infarction (%)	Frequency of DCT (%)	Frequency of ICH (%)	Frequency of CVT (%)	Frequency of SAH (%)
Pfister et al (1992)	Case series, prospective, single center	Radiological abnormalities on CT and angiography	9/86 (10%)		1/86 (1%)	4/86 (5%)	
Kastenbauer et al (2003)	Case series, Retrospective, multicenter	Focal neurological signs with CT abnormalities	19/87 (22%)		6/87 (7%)	9/87(10%)	4/87 (5%)
Katchanov et al (2010)	Case series, prospective, single center	MRI-DWI abnormalities	6/68 (9%)				
Klein et al (2011)	Case series, retrospective, single center	Radiological abnormalities on neuroimaging	16/94 (17%)				
Schut et al (2012)	Cohort, prospective, nationwide	Clinical criteria with or without radiological abnormalities on neuroimaging	174/696 (25%)				
Mook-Kanamori et al (2012)	Cohort, prospective, nationwide	Radiological abnormalities on CT			19/860 (2%)		5/860 (1%)
Lucas et al (2013)	Cohort, prospective, nationwide	Clinical criteria with radiological abnormalities on neuroimaging		11/1032 (1%)			
Bodilsen et al (2014)	Cohort, retrospective, multicenter	Recent radiological abnormalities	19/152 (13%)		6/152 (4%)		1/152 (1%)
Gallegos et al (2018)	Cohort, retrospective, multicenter	Radiological abnormalities on repeated neuroimaging		5/120 (4%)		1/120 (1%)	
Boix-Palop et al (2020)	Cohort, retrospective, multicenter	Clinical criteria with radiological abnormalities on neuroimaging and/or pathological abnormalities		17/162 (10%)			
Deliran et al (2022)	Cohort, prospective, nationwide	Radiological abnormalities on neuroimaging			44/2306 (2%)		
Deliran et al (2020)	Cohort, prospective, nationwide	Radiological abnormalities on venography				26/220 (1%)	
Deliran et al (2022)	Cohort, prospective, nationwide	Radiological abnormalities on CT					22/2306 (1%)
Bendaji et al (2023)	Cohort, prospective, multicenter	Clinical or radiological abnormalities on neuroimaging	All CVC combined 128/506 (25%)				

CT indicates CT angiography; CVC, cerebrovascular complication; CVT, cerebral venous thrombosis; DCT, delayed cerebral thrombosis; DWI, diffusion-weighted imaging; MRI, MRI angiography; and SAH, subarachnoid hemorrhage.

originating from cardiac valve vegetation.[36,37] Intracerebral hemorrhage is a major complication in patients with endocarditis[37,38] and is described in up to 80% of these patients.[39] Besides the septic emboli, cerebral small vessel autoimmune vasculitis or *vasa vasorum* embolic processes are also suggested to be the cause of cerebrovascular complications in patients with infectious endocarditis (Table and Figure).[39–42]

CONCLUSIONS

Cerebrovascular complications affect the likelihood of unfavorable outcome, neurological sequelae, and mortality rate in patients with bacterial meningitis.[16,18] Different mechanisms are involved in causing cerebrovascular complications in patients with bacterial meningitis. Vascular inflammation, formation of thrombi, and a secondary inflammatory response to

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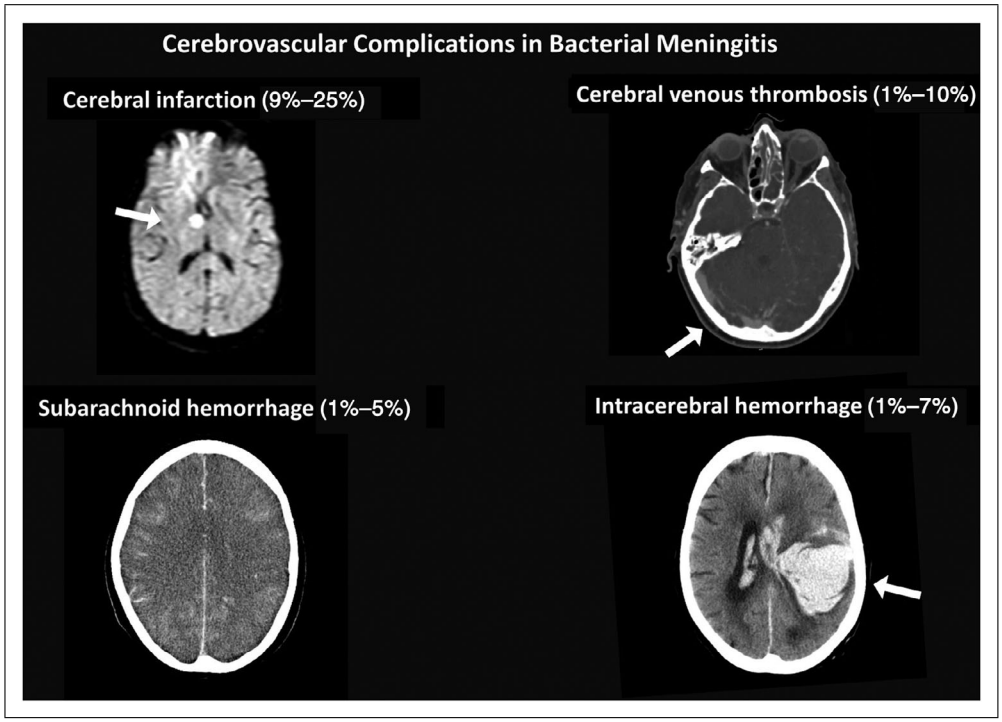

Figure. **Neuroimaging of cerebrovascular complications in bacterial meningitis**.

the endothelial dysfunction, along with inhibition of the fibrinolysis pathway, likely interact together, causing tissue damage [11–14,24] and eventually leading to neurological deficits in these patients.

Unfortunately, there are no established and effective management strategies specifically developed to prevent or treat these specific complications in this patient population. The administration of intravenous thrombolysis in patients with bacterial meningitis complicated by acute ischemic stroke is not advisable. The etiology of stroke in this context is distinct, and the risk of intracerebral hemorrhage is likely considerably higher. Similarly, the use of intra-arterial thrombectomy in patients with bacterial meningitis complicated by cerebral infarction and proximal intracranial arterial occlusion is not routinely recommended.

However, we do recommend conducting neuroimaging in patients with bacterial meningitis and focal neurologic symptoms or altered level of consciousness to identify the underlying cause.

Adjunctive dexamethasone therapy is a recommended approach in patients with bacterial meningitis beyond the neonatal age (from 6 weeks onwards) in regions with advanced medical care.[20] The implementation of adjunctive dexamethasone has contributed to an overall reduction in the incidence of cerebrovascular complications. In cases of proven cerebral vasculitis in patients with bacterial meningitis complicated by stroke, a prolonged dexamethasone treatment of 40 mg daily for 4 days can be considered, followed by slow tapering; however, this is based on expert opinion. Delayed cerebral thrombosis involves a hyperinflammatory syndrome and extensive cerebral infarction occurring days to weeks after an initial period of apparent recovery.[43] There appears to be an association between adjunctive dexamethasone therapy and the occurrence of this devastating complication, as well as an initially elevated level of complement factor C5a.[21] Patients experiencing delayed cerebral thrombosis may require prolonged immunosuppressive treatment, such as an extended course of dexamethasone therapy.[44] Slow tapering dexamethasone afterwards could be implemented.

Currently, there are no established guidelines regarding the use of anticoagulation in patients with cerebral venous thrombosis complicating bacterial meningitis. However, expert advice tends to caution against its use due to the elevated risk of cerebral hemorrhage.[2,45,46] A large international study on cerebral venous sinus thrombosis found the risk of intracerebral hemorrhage to be higher in patients with an infection, however, there was a lack of data to determine if the use of anticoagulation influenced this risk.[47] Further, the surgical treatment of the ear, nose, and throat infection in otogenic bacterial meningitis complicated with cerebral venous sinus thrombosis should always be considered.[29,48–51] The limited availability of studies on subarachnoid hemorrhage complicating bacterial meningitis makes it challenging to establish standardized guidelines for the endovascular treatment of mycotic aneurysms.[7,52,53] In

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patients with bacterial meningitis caused by *S. aureus* cardiology consultation should be a priority to rule out endocarditis.[37]

To reduce the risks of cerebrovascular complications in patients with bacterial meningitis and develop innovative treatment approaches, we require deeper investigations into the underlying pathophysiological mechanisms of the disease. Studies with computed tomography or magnetic resonance angiography in all patients with bacterial meningitis are a good start, where we can compare the outcome and radiological findings between patients with and without cerebrovascular complications on a larger scale. Genome-wide association studies should valuate genetic regions of interest associated with the development of cerebrovascular complication in patients with bacterial meningitis. Identified regions should be evaluated functionally using patient samples and animal studies. Additional autopsy studies will be helpful to comprehend the changes at tissue level. Exploring the potential benefits of blocking the complement component C5a is a promising avenue for research.[54] Recent randomized clinical trials have demonstrated the advantages of a novel antibody that blocks C5a in patients with severe COVID-19.[55,56] This success suggests that similar approaches may hold promise for patients with cerebrovascular complications in bacterial meningitis. By pursuing these avenues of research, we can advance our understanding of the underlying mechanisms and potentially develop innovative therapeutic interventions for individuals affected by cerebrovascular complications in bacterial meningitis.

LIMITATIONS

The main limitation in this narrative review is the shortage of prior original studies on cerebrovascular complications in bacterial meningitis, particularly regarding patients with intracerebral hemorrhage. Combining different types of study designs in this paper makes the data less homogeneous. The use of various neuroimaging modalities, such as computed tomography versus magnetic resonance imaging, poses challenges for data comparison. For instance, magnetic resonance imaging can detect smaller radiological abnormalities like small cerebral infarctions, complicating the comparison.

Furthermore, we believe that very severely affected patients with bacterial meningitis who died early during the clinical course are probably not included in the most conducted studies. These patients probably have higher percentages of cerebrovascular complications that the rest of the patients, leading to underreporting.

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Disclosures

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